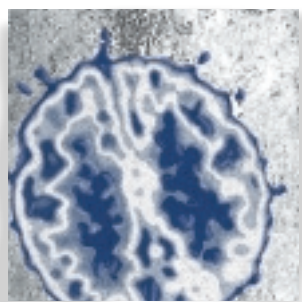


Psychosis related to neurological conditions: pro and cons of the dis- / mis-connectivity models of schizophrenia

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Schizophrenia is still a condition with obscure causes and psychopathology. This paper aims to discuss the “dis-connectivity” hypothesis in relation to some neurological conditions which are known to alter brain connectivity, as well as mimicking some aspects of the disorder. After a short historical introduction to the concept, we will examine the evidence for connectivity problems in schizophrenia, separating the anatomical level from the functional level. Then, we will discuss three different issues concerning connectivity: i) local reduction in connectivity without neuronal loss (within the gray matter); ii) reduction in or alteration of long-range connectivity (within the white matter); and iii) abnormal targets for connections. For each of these aspects, we will look at the conditions able to reproduce anomalies capable of increasing susceptibility to schizophrenia. We conclude that psychosis is more likely to occur: i) when long-range connectivity is concerned; ii) when lesions result in lengthening and scattering of conduction times; and iii) when there are high dopamine levels, shedding light on or adding weight to the idea of an interaction between dopamine and connectivity.

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A long time ago...

The idea that schizophrenia could be related to problems of connectivity can be traced back to the 19th century. It was founded on theories concerning the way the brain was thought to work, at a time when the neuron had not yet been identified. In the very beginning were the associationist philosophical views (James and John Stuart Mill), which stated that concepts and ideas were associated with each other by a sort of affinity mirroring the real world: the idea of a horse was associated with that of the rider. The influential German psychologist, Wilhelm Wundt, who set up the first psychological laboratory, stated that this principle was based on biological foundations.¹ In line with this thinking, Karl Wernicke hypothesized that the disruption of connections between the two language centers (Broca's area and the area he described, Wernicke's area) could also provoke a particular kind of aphasia: conduction aphasia. The confirmation of this theoretical prediction by later observations encouraged him to go beyond this and apply his concept to psychiatric disorders. He proposed that these disorders were related to abnormal conduction between different areas of the cortex. He postulated a disruption in the “psychischen Reflexbogen” (psychical reflex arc) that he named “sejunction.” However, schizophrenia had not yet been described at that time.² The building up of the current nosologic category stemmed

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Selected abbreviations and acronyms

AIDS	<i>acquired immune deficiency syndrome</i>
ALD	<i>adrenoleukodystrophy</i>
EEG	<i>electroencephalography</i>
fMRI	<i>functional magnetic resonance imaging</i>
MLD	<i>metachromatic leukodystrophy</i>
MS	<i>multiple sclerosis</i>
WM	<i>white matter</i>

from the work of Emil Kraepelin at the turn of the 20th century.³ Otto Gross, a young physician, proposed that “dementia praecox” could be related to a sejunction problem, and coined the term “dementia sejunctiva.”⁴ Gross was working in the Burghölzli at the time when Eugen Bleuler was its director. He was influenced by the associationist view of Bleuler, who tried to identify the fundamental psychological disorder as a problem of the relationship between ideas or concepts: “der spaltung” (dissociation – however, this should not be confused with the notion of “dissociating disorder” as described in the *Diagnostic and Statistical Manual of Mental Disorders [DSM]*).⁵ According to the common view at that time, which considered that psychology was closely related to physiology, Gross merged the sejunction concept with that of dissociation.

What makes us now think that schizophrenia is related to connectivity?

We will separate two notions generally confounded in the literature: anatomical and functional connectivity. The rationale for this is that we suppose the latter to be related to the common pathophysiological pathway leading to the clinical expression of the disease. The anatomical aspect is assumed to be one of the possible causes for the dysfunction. We will also discuss two levels of connectivity: a local level, mainly concerning the direct surroundings of the neurons in the gray matter, and a long-range level, mainly concerning the white fiber tracts connecting distant parts of the brain. A third anomaly of connectivity could be related to neurons connecting with erroneous targets.

Gray matter connectivity

Gray matter hypotrophy and atrophy have both been described in schizophrenic patients. Hypotrophy refers to a congenital reduction in the quantity of gray matter.

It has been shown that such a reduction exists in patients as early as the first episode, with the most robust evidence in the external temporal lobe, but with reductions also in the hippocampus and frontal and parietal lobes.⁶ However, it might be that part of the reduction is already related to an earlier origin of the disorder. Indeed, the average duration of untreated psychosis is 2.4 years, and some markers can even be traced back to the disease process long before that.⁷ However, the presence of similar, although lesser, gray matter reduction in relatives of patients also speaks for a congenital problem. Atrophy refers to an acquired reduction in gray matter. The acceleration of gray matter decrease seems to occur mainly during the first year(s) of the disease process. Later on, the slope of the decrement is less striking.

This gray matter reduction does not seem to be related to neuronal loss occurring after the second trimester. Indeed, only a few studies have found evidence for gliosis, a reputedly robust marker of neuronal necrosis, in the brains of patients with schizophrenia.^{8,9} It might be possible that some neurons are lost by apoptosis not necessarily accompanied by gliosis, but the general consensus is that most gray matter atrophy represents a reduction in neuronal volume.¹⁰ As a matter of fact, cortical neurons are generally described as being smaller with higher density in pathological studies. Many authors have pointed out that the compartment showing the larger reduction could be the volume of axons and dendrites. In other words, there should be a reduction in the connecting parts of the neurons. In line with these arguments, synaptic spines and synaptic markers are reduced,¹¹ as well as synaptic gene expression.¹²

In short, there is evidence of a reduction in local connectivity in some cortical areas in schizophrenia.

White matter connectivity

There are also reasons to believe that the support of long-range connectivity, namely that of white matter, is also abnormal in schizophrenia. Although there is no direct proof, it is probable that the dilatation of the anterior horn of the lateral ventricle, one of the most robust findings in schizophrenia,¹³ has something to do with a volume reduction of frontal white matter. Here again, it seems to be a case of hypotrophy as well as atrophy.¹⁴ Voxel-based morphometry has mainly highlighted the probability of a reduction in white matter in the subcortical frontal region and the corpus callosum. Abnormal

microscopic organization of white matter has been repeatedly described with diffusion tensor imaging (DTI), although multiple and not overlapping areas were concerned in the studies.^{15,16} Reduced myelinization has also been suggested due to signal reduction in magnetization transfer imaging.¹⁷ This is in accordance with phosphorous magnetic resonance spectroscopy showing an increased breakdown of phospholipids at the onset of the disorder (increased phospholipids in patients at the first episode)^{18,19} and a pervasive reduction in synthesis (reduction in phosphomonoester)²⁰⁻²² in the prefrontal region. The latest evidence for white matter decrease comes from the observation of a reduction in oligodendrocyte gene expression.²³⁻²⁵

In brief, there is also substantial support for a reduction in long-range connectivity.

Erroneous connections

In about 30% of schizophrenic patients, persistent subplate neurons have been found.^{26,27} As their disappearance is important for the maturation of thalamocortical connections, some authors have raised the point that this might be an example of erroneous connections, ie, persistent connection with subplate instead of layer 4 neurons. Pyramidal cell disarray in internal temporal cortices²⁸ could also be accompanied by such abnormalities of connectivity. However, many of these results have been hard to replicate, and the false target hypothesis remains speculative, although interesting to look into.

Both local and long-range reductions in anatomical connectivity, together with possible erroneous connections, have led several authors to rejuvenate the “sejunction hypothesis” under the updated appellation of disconnectivity.^{27,29-33}

A disorder of functional integration?

The functional counterpart of these anatomical disorders could be an abnormal coordination between neurons of the same (local) and/or distant (long-range) areas. Functional integration is thought to allow segregated neurons to interact as a global assembly. Such a process is supposed to allow information to be streamed and bound into the coherent whole that we experience as consciousness.³⁴⁻³⁶ It is viable to think that this could be the process which breaks down in schizophrenic patients.^{37,38}

An initial way to assess integration is by functional connectivity, defined as the amount of dependency between pairs of regions.^{39,40} Using functional magnetic resonance imaging (fMRI), electroencephalography (EEG), or magnetoencephalography (MEG) data, studies generally show that anteroposterior connectivity is deficient.⁴¹⁻⁴³ Moreover, these findings have been associated with symptoms. In one fMRI study⁴⁴ and two EEG studies,^{45,46} it was outlined that the less the frontal cortex was functionally dependent on the temporal cortex, the more the subject was prone to verbal hallucinations (trait studies). Recently we had the opportunity to assess a patient who signaled his hallucinations during an fMRI session. Though these two areas were normally functionally connected during his resting state, their connectivity vanished during the hallucinations (state study).

However, it is not as simple as a pure equivalence between reduced anatomical connectivity and reduced functional connectivity. Indeed, in a very reproducible way, bilateral functional connectivity is found to be increased.⁴⁷⁻⁵¹ This is especially true between the two frontal lobes despite abnormal or reduced colossal fibers. It can be argued that, whereas the first anomaly is a primary deficit, the increased functional connectivity between the frontal lobes could be a secondary abnormality, eg, a compensatory recruitment for better control over the posterior instrumental regions.³⁸

A second way to assess functional integration is at the whole brain level, not only between pairs of areas. It has been proposed that areas of coherent activity form an integrated “core” while the “rest” of the brain is supposed not to interact with this core, to avoid disturbing its activity. Such core-rest structure is said to be dynamic, ie, susceptible to change from time to time, and to correspond to the network of areas supporting the conscious present.³⁶ In two fMRI studies and one MEG study, during different executive tasks, the “cores” of patients were not different from those of controls, neither in their anatomical distribution, nor in their global integration value. This did not prevent the abovementioned abnormality of functional connectivity. In other words, integration was distributed differently within the “core” of patients (less in the anteroposterior axis, more in the left-right axis). However, the “rest” of the brain, ie, regions not taking part in the ongoing activity, could also play a role in the anomaly of global brain functioning. Indeed, “rest” interacted with the core in such a way that this uncontrolled activity interfered with that of the “core.”

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This noise could potentially affect coherent brain functioning, as it was correlated with the degree of negative symptoms.³⁸

In short, anatomical and functional levels should not be confounded, as they might give opposite results, eg, between the two frontal lobes. However, an anatomical connectivity deficit could potentially subtend some of the anomalies in the observed functional integration, which could reflect the patient's information-processing problem.

Neurological diseases could help refine the model

The disconnectivity hypothesis causing functional disintegration is a promising pathophysiology for schizophrenia. But what is the most important anomaly? There are multiple levels of connectivity that could be discussed, but we will focus on:

- A reduction in local connectivity, without neuronal loss.
- Anomalies of long-range connectivity.
- Abnormal connection between neurons which should not be connected.

The term deconnection will refer to a reduction in connectivity. Disconnectivity will be used when the main effect of the lesion results in lengthening or scattering of the conduction time. Finally, we will speak about misconnectivity when connections are erroneous, ie, between two neurons which should not be connected. The reader should be warned that this is not the way other authors use these terms, which are generally considered to be interchangeable.^{33,52}

Local (intracortical) connectivity

There is a lack of neurological models of reduced local connectivity without neural loss. However, such models can be easily obtained by an impoverished environment.⁵³ For example, breeding rats without social interactions induces cortical shrinkage. This does not correspond to neuronal loss, but to a reduction in neuropiles and synapses.^{54,55} The same phenomenon of related gray matter adaptation to training is likely to also occur in man. Indeed, the size of the posterior hippocampus has been showed to be increased in London taxi drivers, probably because of job-related overuse.^{56,57} We recently observed in normal subjects that the more they spontaneously used their memory network, the more gray mat-

ter they had in the stimulated regions. Thus, gray matter volume can adapt, depending on practice (Foucher et al, unpublished material).

Thus, we can use impoverished environment as a model of reduced local connectivity without neuronal loss. Though we lack systematic studies, there is no evidence to date that, without increasing the level of stress, impoverishment is sufficient to increase the risk of schizophrenia. Neither is there any observation of the topography of gray matter reduction in nonpsychiatric subjects living in an impoverished environment. However, turning the question around, the observation that environmental factors possibly induce cortical atrophy could lead to another interpretation of the anatomical problem in patients. It may be that some of the gray matter reduction observed in patients corresponds to their way of living, eg, avoiding social contact could simulate the cortical shrinkage seen in rats after social deprivation.¹⁰ In fact, it might be that the so-called hypotrophy could be explained in the same way. Relatives could display gray matter reduction because of behavior related to an overt or subclinical schizoid or schizotypal personality disorder. There is much less argument for environmental effect on white matter, but one should consider looking at it more closely.

In short, there is no evidence that a reduction in local connectivity alone could provoke schizophrenia. But it could be that the impoverishment model does not replicate schizophrenic pathology, eg, the defect of anatomical local connectivity could concern selective synapses such as gamma-aminobutyric acid (GABA) ones.⁵⁸

Long-range connectivity

Multiple models of white matter disorders can be found in neurology. These are the best models of disordered long-range connectivity and they mimic in some way, although to a much larger extent, what has been described in schizophrenia.

Most white matter (WM) diseases are associated with a higher occurrence of psychosis than in the normal population (*Table I*).⁵⁹⁻⁸² This increased prevalence appears to be independent of the etiology, albeit differing largely according to the cause. Late-onset adrenoleukodystrophy (ALD) and metachromatic leukodystrophy (MLD) present a higher occurrence of psychosis.^{61,62,83} Moreover, in such cases psychoses are more likely to occur without confusion.

Is psychosis a specific feature of white matter diseases?

Unfortunately, this does not appear to be the case. Mania and depression are also very frequent in many WM diseases⁶⁰ This illustrates once again the spectrum ranging from bipolar disorder to schizophrenia. However, against such a proposal, it is worth mentioning that late-onset ALD and MLD seem to have some specificity for psychosis. We were not able to find any reports of mania or depression in ALD or MLD through our reading or through Medline searches.

Are white matter diseases more likely to specifically trigger psychosis, or is this feature common whatever the type of encephalopathy?

In many neurodegenerative diseases, eg, metabolic or vascular diseases, psychosis can precede dementia. Some WM diseases also evolve toward a dementia. Thus, it is questionable whether WM diseases have a selective role in provoking psychosis, or whether psychosis is just an early reaction to a nonspecific encephalopathy. Indeed, the comparison with Alzheimer's disease shows

a similar degree of psychosis (a mean of 41 % but up to 60%).⁸⁴ However, the clinical features are very different from the psychosis of schizophrenia:

- Delusions are mostly persecutory (non-bizarre).
- There are typically misidentifications, and if hallucinations occur they are mostly visual.

This is not the case of WM diseases where psychotic symptoms are more similar to schizophrenia (multiple sclerosis, metabolic diseases such as ALD and MLD)⁶²:

- Bizarre delusions leading to odd behavior.
- Verbal hallucinations.

Nevertheless, these psychotic symptoms are not specific to all WM diseases. Indeed, persecutory delusions (non-bizarre) are also characteristic of psychosis in acquired immune deficiency syndrome (AIDS) and normal-pressure hydrocephalus in Binswanger's disease, perhaps in relation to frontal lobe involvement.^{85,86}

Can white matter diseases provoke psychosis whatever the age?

This is clearly not the case. Patients seem to need to be at least adolescents to express a psychosis related to WM dis-

		Psychosis		Mania		Depression	
Immune diseases	Multiple sclerosis	5%	Grant, ⁷⁵ 1986	x 10	Joffe, ⁸⁰ 1987	27-54%	Minden, ⁷⁰ 1990
	Acute disseminated encephalomyelitis		Nasr, ⁷¹ 2000		Paskavitz, ⁸¹ 1995	?	
Metabolic diseases	Adrenoleukodystrophy (late onset)		Rosebush, ⁶² 1999	?		?	
	Metachromatic leukodystrophy	53%	Filley, ⁵⁹ 1992, Hyde, ⁶¹ 1992	?		?	
	B9 or B12 deficiency		Hutto, ⁶⁶ 1997		Hutto, ⁶⁶ 1997		Pennix, ⁷² 2000, Hutto, ⁶⁶ 1997
Vascular diseases	Binswanger's disease – WM dementia		Lawrence, ⁷⁷ 1995	>AD	Bennett, ⁶³ 1994	>AD	Bennett, ⁶³ 1994
	Systemic lupus erythematosus	5-15%	West, ⁷⁸ 1994		West, ⁷⁸ 1994		Wekking, ⁷⁴ 1993
	Post-radiation encephalopathy		Lawrence, ⁷⁷ 1995				
Others	Toluene abuse		Byrne, ⁶⁵ 1991	?			Zur, ⁷⁵ 1990
	Traumatic brain injury (recovery – DAI ?)		McAllister, ⁶⁹ 1992	4%	van Reekum 1994		
	AIDS (acquired ADC)	4%	de Ronchi, ⁷⁹ 2000		Kiebertz, ⁶⁷ 1991	10%	Perry, ⁷³ 1994
	Normal pressure hydrocephalus			Rare	Kwentus, ⁶⁸ 1987		Rice, ⁸⁶ 1973

Table I. Prevalence of psychosis, mania, and depression in several white matter diseases, classified according their etiologies.⁶¹⁻⁸² See text for comments. DAI, diffuse axonal injury; AIDS, acquired immune deficiency syndrome; ADC, AIDS dementia complex; AD, Alzheimer's disease.

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order. Younger patients who present one of the many metabolic WM diseases (Krabbe's, Pelizaeus-Merzbacher, Alexander's, and Cockayne's diseases, ALD, MLD), are generally not reported to manifest psychotic symptoms.^{59,60} Interestingly, in elderly patients, psychosis with clinical features similar to those of schizophrenia is rare, eg, in Binswanger's disease.

This age prevalence could be related to the cause. However, against such an explanation, early forms of MLD or ALD do not present with psychotic features, as seen in late-onset forms.

Why is psychosis age-dependent in white matter diseases?

This age dependence is very much a reminder of the risk window for psychosis in schizophrenia. Whereas negative symptoms do show that the disease lasts beyond the 40s, many patients do not present new psychotic symptoms or disease exacerbation. There are reasons to support a relationship with dopamine. Indeed, dopamine release rises, from a low level in childhood, to a maximum during adolescence and early adulthood, whereas it slowly declines in the late 30s.⁸⁷

This dopaminergic dependence may explain why WM-related psychosis can be well treated by antipsychotics in white matter diseases.⁶⁰

In other words, disconnection per se may not be enough, as it must occur with a sufficient level of dopamine. However, it could be either an important secondary factor by lowering the threshold for expressing psychosis, or even a requirement for expressing psychotic features on dopamine release. This is in line with the observation that only a minority of normal subjects given amphetamine do become psychotic.⁸⁸ In such rare cases a cofactor such as a subnormal disconnectivity may exist. A final explanation could be that WM diseases weaken cortical control over dopamine release in the striatum (or directly on the ventral tegmental neurons). This is expected to be the case if the WM lesion is localized between the frontal lobe and the striatum. However, as will be discussed later, frontal WM lesions are more prone to provoking depression than psychosis.

Can curing the white matter disease improve psychosis?

If this were the case, then it would be a strong argument for a causal role of WM lesions in psychosis.

Positive responses come from case reports in two WM diseases:

- In multiple sclerosis (MS) where two patients with psychotic features resolved their symptoms after a cure of corticoids.⁸⁹
- In normal-pressure hydrocephalus, shunt placement allowed psychosis recovery, from substantial to complete.^{85,86}

Does a specific location of white matter disease provoke psychosis?

ALD and MLD are not very informative, since WM anomalies are essentially diffuse and can originate in any part of the brain. In these diseases there is no reported correlation between psychotic symptoms and a lobar predominance. In MS, two studies consistently demonstrated that demyelination located in the temporal lobe were more common in patients developing psychosis.^{90,91} Contrary to what could be expected, frontal location is not very likely to be associated with psychosis. It is more frequently accompanied by depression in MS,⁹² but also in WM dementia (eg, in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy [CADASIL]).^{93,94} This could be a reminder of the hypothesis that links frontal lobe hypofunction to the psychomotor retardation shared by depression and schizophrenia.⁹⁵

Lesions may be located within the cortex, in the subcortical region, or around the ventricles. Subcortical lesions would preferentially affect U-fibers connecting adjacent cortex, while deeper lesions would disturb long-range connections. In MLD, it has been proposed that cortical demyelination could explain the high rate of psychosis observed in this disease.⁹⁶ Against such a proposal, it is worth remembering that cortical involvement could also be seen in MS, where it mainly provokes seizures without reported psychosis.⁹⁷ Seizures also appear in the evolution of MLD, but after several years of psychosis. In MS, seizures are not associated with the occurrence of psychosis. Thus, cortex might not be the primary site for provoking psychosis. Lastly, MLD, like MS, mainly affects long-range connections while sparing U-fibers connecting adjacent areas.⁹⁸

A personal observation also makes us favor long-distance connection as a primary site for psychosis. The patient, a 45-year-old woman, had undergone, 15 years before presentation, irradiation for a low-grade glioma

in the left inferior temporal lobe. She developed a post-radiation leukoencephalopathy, mainly affecting the arcuate fasciculus connecting Broca's and Wernicke's areas. She was admitted for continuous verbal hallucinations in the form of the voice of a child speaking behind her, on her right side. She was so convinced of the existence of the child that she sometimes shouted at "him" during the examination, telling "him" to "shut up." The symptoms quickly resolved with 5 mg of haloperidol. This clinical vignette fits in well with trait and state functional studies of hallucinations, all showing a reduction in functional connectivity between Wernicke's and Broca's areas.⁴⁴⁻⁴⁶ Moreover, in one study of white matter in schizophrenic patients, fibers seemed to be less well oriented in the arcuate fasciculus of hallucinating patients compared with controls. However, non-hallucinating patients presented with even worse orientation indices, which does not support our view (fractional anisotropy using DTI⁹⁹).

Do white matter diseases also reproduce other features of schizophrenia?

Although psychosis is a characteristic feature of schizophrenia, it is not specific and not isolated. One of the other features is disorganization. Unfortunately there is no clear report of disorganization in WM diseases. This could be related to a reporting bias, as neurologists may not recognize or describe mild disorganization. Indeed, we were able to observe one patient scoring 4 on the Positive And Negative Syndrome Scale (PANSS) disorganization subscore. The symptom lasted during a relapse of her MS, and was accompanied by a clear reduction in executive attention without confusion or mood disorder. However, more observations are required in order to conclude.

It is even more difficult to conclude concerning negative symptoms which are also an important feature of schizophrenia, because they can be misidentified with depression or cognitive decline.

What kind of white matter lesion is most likely to evoke psychosis?

WM lesions can have two different physiological effects:

- From reduction to absence of conduction between two areas. This concept is closer to the notion of disconnection.

- A variation in conduction time between the different axons linking the two areas. This is what we termed "disconnection." Synapses will not be active in the same time window, resulting in an improper summation in the postsynaptic neurons. Not only will the message be weakened, but it will also be noisier.

MS and MLD essentially result in lengthening and scattering of conduction delays.¹⁰⁰ Demyelinating diseases can also induce voltage-gated channel anomalies that result in conduction bloc (analogous to disconnection).¹⁰¹ However, MS and MLD seem to trigger more psychotic episodes than diffuse axonal injury after a head trauma that basically results in a disconnection.¹⁰² Accordingly, there is modest evidence that a dis-synchrony between axons better accounts for psychosis.

Misconnectivity

Misconnectivity is perhaps even more difficult to model, because it can involve different neurons. However, multiple neurological diseases come with putative misconnectivity, especially when accompanied by cortical dysplasia or heterotopia. Some of them have been described as presenting with psychosis:

- Schizencephaly-polymicrogyria.¹⁰³
- Ito's disease.¹⁰⁴
- Facomatosis as tuberous sclerosis, also termed Bourneville's disease.¹⁰⁵ In another facomatosis, neurofibromatosis type 1, or Recklinghausen's disease, about 3% to 6% of patients develop psychosis.^{106,107}

However the amount of psychosis in misconnection diseases is mild. It could also not be the causal factor, as most of these disorders are accompanied by epilepsy. But from an other perspective, the psychosis of epilepsy has not been found to be related to dysplasia.¹⁰⁸ Another confounding factor could be the presence of WM lesions in most misconnection diseases. As an example, both tuberous sclerosis and neurofibromatosis also come with WM abnormalities that could account for the expression of psychosis.¹⁰⁹⁻¹¹⁰

Interestingly, psychosis related to cortical dysplasia can appear earlier than adolescence.¹⁰⁶ According to our previous line of reasoning, this could mean that dopamine is not an important cofactor. However, as far as we know, psychosis related to dysplasia can also be treated by neuroleptics.

In short, there is little to modest evidence that misconnection could result in psychosis.

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Conclusion

No firm conclusions can be derived from this comparative nosology analysis, but lines of evidence are emerging. Neurological diseases essentially support the idea that long-range connectivity rather than local connectivity or misconnectivity could be an important cofactor in

the expression of psychotic symptoms. The most important effect is likely to lengthen and scatter the conduction time (disconnectivity) rather than merely diminishing it (deconnectivity). Lastly, both WM lesions and a sufficient amount of dopamine seem to be required for the expression of psychosis, as the cure of one or the other is sufficient to alleviate the symptoms. □

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Psicosis relacionada con las alteraciones neurológicas: pros y contras de los modelos de conectividad errónea en la esquizofrenia

La esquizofrenia sigue siendo un trastorno de causas y psicopatología oscuras. En este trabajo se comenta la hipótesis de la "conectividad errónea" relacionada con algunos trastornos neurológicos que alteran las comunicaciones cerebrales o que remedan ciertos aspectos del trastorno. Después de una breve introducción histórica del concepto examinaremos las pruebas acerca de los problemas de conectividad en la esquizofrenia, separando el plano anatómico del funcional. Seguidamente, expondremos tres cuestiones distintas sobre conectividad: i) reducción local de la conectividad sin destrucción neuronal (dentro de la sustancia gris); ii) reducción o alteración de la conectividad de largo alcance (dentro de la sustancia blanca); e iii) objetivos anómalos de las comunicaciones. Para cada uno de estos aspectos indagaremos los trastornos que reproducen anomalías que, a su vez, aumentan la tendencia a la esquizofrenia. Concluimos que la probabilidad de psicosis aumenta: i) cuando se afecta una vía de largo alcance, ii) cuando las lesiones producen tiempos de conducción más largos y dispersos; e iii) cuando existen valores elevados de dopamina, lo que arroja luz o añade pruebas a la idea de una interacción entre la dopamina y la conectividad.

Psychose liée aux troubles neurologiques : pour ou contre les modèles de dis-/misconnectivité dans la schizophrénie ?

Cet article discute l'hypothèse de disconnectivité comme étiologie possible de la schizophrénie. Un rapide survol historique permettra de rappeler que même présentée comme hypothèse récente, il ne s'agit que d'une réinvention d'idées qui ont plus d'un siècle. Puis nous discuterons des conséquences physiologiques attendues. Enfin, nous ferons le tour des pathologies neurologiques pouvant s'offrir comme modèle d'atteinte de la connectivité. Nous tenterons de déterminer sur la base de la littérature dans quelle proportion ces atteintes peuvent mimer la pathologie, en fait essentiellement les troubles psychotiques, puisque les symptômes négatifs, voir la désorganisation sont essentiellement rapportés comme des troubles cognitifs dans la littérature neurologique. Les pathologies de la connectivité seront regroupées selon trois catégories: 1) une réduction de la connectivité locale (à l'intérieur de la matière grise), sans perte neuronale, 2) une réduction ou une altération de la connectivité longue distance (atteinte de la substance blanche), 3) des anomalies de cible, autrement dit des neurones qui ne se connectent pas à la bonne cible. Sans que l'on puisse tirer de conclusions définitives, il semble que les troubles psychotiques aient d'autant plus de chance d'apparaître, 1) que la connectivité longue distance est altérée, 2) que les lésions s'accompagnent d'une disparité des temps de conduction, 3) que le niveau de dopamine est élevé, ce facteur semblant agir de façon indépendante.

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